

# Low serum cholesterol concentration and serotonin metabolism in men

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Recent findings suggest a relationship between low serum cholesterol concentrations and risk of death from violent causes, notably suicide.<sup>1,2</sup> To explain a possible association between low cholesterol and violent death, a role for serotonin metabolism was suggested by Engelberg and subsequently elaborated by Salter.<sup>3,4</sup> According to these views low cholesterol may be accompanied by a decrease in serum free tryptophan. As a consequence there is less supply of this amino acid to the brain, where it is used to synthesise serotonin. Low serotonin concentrations have been observed in depression and suicide. To our knowledge, no studies have been reported on serotonin metabolism and its relation to cholesterol levels in humans.

We assessed whether serotonin metabolism is different in subjects with chronically low serum cholesterol concentrations by comparing serotonin in healthy middle aged men with low serum cholesterol concentrations (4.5 mmol/l or lower) and a reference group with concentrations between 6.0 and 7.0 mmol/l.

## Subjects, methods, and results

A cholesterol screening study among 30 359 men aged 40-70 was conducted in Rotterdam in 1990-1. Non-fasting blood samples were obtained and cholesterol was measured enzymatically. Men with a serum cholesterol concentration below the fifth centile (4.5 mmol/l or lower) were invited to have a second measurement in 1993-4 unless they used antidiabetic or cholesterol lowering drugs or had renal or thyroidal diseases or cancer. If the overnight fasting cholesterol concentration was again 4.5 mmol/l or lower they were entered in the study. The reference group consisted of

men with cholesterol concentrations between the 35th and 75th centiles (6-7 mmol/l) both in 1990-1 and in 1993-4. The two groups were individually matched for age and, as an index for socioeconomic status, postal code.

Plasma and platelet serotonin concentrations were measured with reversed phase high performance liquid chromatography with electrochemical detection. The dissociation constant ( $K_d$ , in nmol/l) and the maximal number of binding sites for serotonin on platelets ( $B_{max}$ , in fmol/mg protein) were also measured. Plasma and platelet serotonin concentrations were measured in 100 matched pairs, and serotonin binding was measured in a random subsample of 50 pairs.

Differences in mean values of continuous variables between the groups were analysed with paired *t* tests. As plasma serotonin showed a skewed distribution, plasma concentration was analysed after natural logarithmic transformation. In case of dichotomous variables McNemar's test was used.

The table shows general characteristics and serotonin measures in men with low cholesterol and the reference group. The plasma serotonin distribution in subjects with low cholesterol concentrations was shifted towards the left, with a mean difference compared with the reference group of 1.8 nmol/l. In the low cholesterol group the geometric mean was 21.3% lower than in the reference group ( $P=0.03$ ; 95% confidence interval 2.0% to 37.4%). Other measures of serotonin metabolism showed no difference.

## Comment

We found that plasma serotonin concentrations are lower in untreated men with persistently low serum cholesterol concentrations ( $\leq 4.5$  mmol/l) than in a reference group. This supports the hypothesis that serotonin metabolism may be implicated in the observed association between low cholesterol concentrations, behavioural changes, and violent death.

The serotonin variables we determined are indirect measures of central nervous system serotonin activity, believed to be involved in the increased risk of violent death. Although plasma and platelet serotonin indices are an accepted model for serotonergic brain neurones, this has limitations that may partly explain the lack of an association of low cholesterol concentrations with platelet serotonin concentrations or serotonin binding as measured in our study. Our finding of lower plasma serotonin concentrations in men with low cholesterol, however, indicates that serotonin metabolism is altered in these subjects.

To our knowledge, this is the first study in humans investigating the relation of serum cholesterol and serotonin metabolism. One study in monkeys showed animals with low cholesterol to have lower central nervous system serotonin activity.<sup>5</sup> The implications of these findings are unclear, however, as these animals had their cholesterol concentration lowered or increased during dietary intervention.

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Conflict of interest: None.

**Table 1—General characteristics and serotonin measures in men with chronically low cholesterol concentrations ( $\leq 4.5$  mmol/l) and in a reference group with cholesterol concentrations between 6.0 and 7.0 mmol/l. Values are means (SE) unless stated otherwise**

	Low cholesterol group (n=100)	Reference group (n=100)	P value
<b>General characteristics</b>			
Age (years)*	55.0 (1.0)	54.9 (1.0)	
Body mass index (kg/m <sup>2</sup> )	24.5 (0.3)	24.6 (0.3)	0.86
Weight loss $\geq 5\%$ in last six months (%)	6.0	4.0	0.74
Diastolic blood pressure (mm Hg)	85.7 (1.1)	85.5 (1.1)	0.93
Systolic blood pressure (mm Hg)	134.8 (1.9)	136.1 (1.8)	0.77
Serum cholesterol concentration (mmol/l)†	3.8 (0.05)	6.5 (0.05)	
Smoking (%)	44	41	0.73
Energy intake (kJ/day)	11 375 (350)	10 850 (340)	0.23
Alcohol intake (g/day)	13.1 (1.8)	21.9 (2.5)	0.01
Fat intake (g/day)	112.6 (4.6)	104.4 (4.3)	0.13
Family history of depression or suicide (%)	8.0	8.0	1.0
History of psychiatric disease‡ (%)	4.0	7.0	0.82
<b>Measures of serotonin metabolism</b>			
Plasma serotonin concentration (nmol/l)	9.31 (0.77)	11.10 (0.72)	0.03
Platelet serotonin concentration (nmol/10 <sup>6</sup> platelets)	2.94 (0.10)	3.01 (0.12)	0.77
Dissociation constant (nmol/l)	0.12 (0.01)	0.12 (0.01)	0.60
Platelet serotonin uptake capacity (fmol/mg protein)	2103 (81)	2148 (103)	0.49

\*Age was a matching factor.

†Selection based on serum cholesterol concentrations.

‡Self reported history of depression, treatment by a psychiatrist, or suicide attempt.

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